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EXAMINER	
JAISLE, CECILIA M	
ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
05/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,494	ST-DENIS, YVES	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,10 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 13 & 17* is/are rejected.

7)☒ Claim(s) *1,2,4,10 and 12-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-18-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Applicants' election of the invention of Group IV without traverse in the Response of Feb. 4, 2008 is acknowledged. Claims 1-2, 4, 10 and 12-17 are under examination.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for CFR binding activity *in vitro* and CFR functional assay *in vitro*, does not reasonably provide enablement for treatment of depression or anxiety (claim 12), or IBS (claim 13). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not provide competent evidence that the instantly disclosed tests are predictive of all uses disclosed and embraced by the claims for the intended host.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This application's disclosure is insufficient to enable the instantly claimed methods based solely on *in vitro* inhibition of CRF activity. The state of the art indicates the requirement for undue experimentation.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

(1) Breadth of claims.

(a) Scope of the compounds. The claims cover potentially billions of pyrido-pyrimidines of Formula (I).

(b) Scope of the diseases covered. Treatment of depression, anxiety and IBS.

(2) The nature of the invention and predictability in the art: Therapeutic use of novel compounds in treating depression, anxiety and IBS. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher,* 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information is so meager, that it would require extensive experimentation to determine a specific dosage for a specific recited disease, mode of administration and therapeutic regimen. Moreover, the dosage is generic; the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for various types of conditions and diseases. No dosage or therapeutic regimen is present to direct the skilled artisan to treat a potential host suffering from depression, anxiety and IBS.

(4) State of the Prior Art: This record does not recognize any pyrimido-pyridines structurally related to the compounds of Formula (I) that have been used for the treatment of all of depression, anxiety and IBS.

Arborelius reports "the hypothesis that CRF receptor antagonists may represent a novel class of antidepressants and/or anxiolytics." Zorrilla reports "the hypothesis that CRF antagonists may be useful for the pharmacotherapy of pathological anxiety." Taché suggests, "Targeting CRF1-dependent pathways may have potential benefit against stress or anxiety-/depression-related functional bowel disorders."

The ability of a compound that inhibits CRF activity to treat depression, anxiety and IBS is open to proof.

(5) Working Examples: No disclosure correlates *in vitro* results to *in vivo* prevention and treatment of those conditions specifically named. The specification prophesies that the methods will treat depression, anxiety and IBS, but no working examples actually show treatment of a single condition specifically attributable to CRF activity.

The specification discloses that the compounds of formula (I) function by inhibiting all CRF activity associated with a debilitating condition, for which Applicants provide no competent evidence. Furthermore, Applicants have not provided competent evidence of known tests that are highly predictive for CRF activity by the claim language for the intended host or specifically for treatment of depression, anxiety and IBS.

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. 112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Syst. v. DeKalb Genet., 65 USPQ2d 1452, 1456 (Fed. Cir. 2003). "[T]he scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(6) Skill of those in the art: See the discussion above of Arborelius, Zorrilla and Taché. The state of the art supports that successful treatment of all conditions mediated by CRF is subject to further investigation.

(7) The quantity of experimentation needed: Based on the disclosure content, to use the invention would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

The discussion of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breath of the claims, the pharmaceutical nature of the invention, the unpredictability of relationship between kinase activity and prevention and treatment of all diseases, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

Response to Feb. 4, 2008 Remarks

Regarding treatment of anxiety and depression, Gillian (an Applicant cite) concludes with a call to further research: "The initial clinical trials with CRF1 receptor

antagonists in the next few years will be critical developments in the research area, and if successful, these agents could revolutionize the treatment of anxiety or depression."

Zorilla (an examiner cite) hypothesizes use of CRF1 receptor antagonists in anxiety treatment: "Collectively, these findings support the hypothesis that CRF1 receptor antagonists may be useful tools for the pharmacotherapy of pathological anxiety."

The study by Zobel (cited by Applicants) of R121919 as a potential anxiolytic is interesting, but note that the decision by Janssen Pharmaceutica (Neurocrine Announces that Janssen Pharmaceutica Intends to Replace R121919 With A Back-Up Compound, Business Wire, 04-05-00, http://findarticles.com/p/articles/mi_m0EIN/is_2000_April_5/ai_61303934, downloaded 5/18/2008) "…to discontinue further development of R121919 was based on observations of reversible increases in liver enzymes in two volunteers participating in an expanded safety trial conducted in the United Kingdom."

Tache (cited by the examiner) concludes with the recognition of the need for more research, "These findings support the concept that hyperactivity of the CRF system, presumable the CRF1-dependent pathways, contributes to the comorbidity of anxiety-depression with colonic symptoms in diarrhea predominant IBS patients. Strategies primarily targeted against CRF1 receptors may provide insight into their role in IBS symptoms and a new therapeutic venue for IBS."

Accordingly, a fair assessment of the current medical literature supports the position that the present specification does not enable the use of the presently claimed methods in treatment of depression, anxiety or IBS.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following recitations fail to particularly point out and distinctly claim the subject matter of the intended reaction:

"an amine," "the amino group" - There is no indication of the source and/or identity of the intended amine.

"basic conditions" – This fails to define the intended reagent; it is inclusive of many compounds that may be variously defined:

- Arrhenius base: a substance that increases the concentration of hydroxide ions when dissolved in water. This definition limits bases to substances that can dissolve in water.
- Brønsted-Lowry base: a proton acceptor.
- Lewis base: an electron-pair donor.

"a protecting group" - Is introduced into a molecule by chemical modification of a functional group in order to obtain chemoselectivity in a subsequent chemical reaction. Amines may be protected by:

- Carbobenzyloxy (Cbz) or Benzyl (Bn) group - Removed by hydrogenolysis

- *tert*-Butyloxycarbonyl (BOC) group - Removed by concentrated, strong acid (e.g., HCl or CF_3COOH)

- 9-Fluorenylmethyloxycarbonyl (FMOC) group - Removed by base, e.g., piperidine.

- *p*-methoxyphenyl (PMP) group - Removed by Ammonium cerium(IV) nitrate (CAN)

"the double bond" – It is not possible to determine which double bond is intended, as several double bonds may be present.

"an oxidizing agent" - An oxidizing agent can be defined as either a chemical compound that readily transfers oxygen atoms, or a substance that gains electrons in a redox chemical reaction.

"the aldehyde of compounds (V)" – It is not possible if this term means that compound (V) is intended to be an aldehyde itself, or if compound (V) is somehow to be modified to have an additional aldehyde group.

"Wittig reaction" - A chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide to give an alkene and triphenylphosphine oxide. There is no indication of the source or identity of the phosphonium ylide needed for the reaction.

"acid hydrolysis" - Acid includes many compounds that may be variously defined:

- Arrhenius acid: a substance that increases the concentration of hydronium ion when dissolved in water. This definition limits acids to substances that can dissolve in water.
- Brønsted-Lowry acid: a proton donor.
- Lewis acid: an electron-pair acceptor.

"the alcohol of compounds (VIII)" - It is not possible to determine if this term means that compound (VIII) is intended to be an alcohol itself, or if compound (VIII) is somehow to be modified to have an additional alcohol group.

"a reducing agent" - A reducing agent (reductant or reducer) is the element or a compound in a redox (reduction-oxidation) reaction that reduces another species. n doing so, it becomes oxidized, and is therefore the electron donor in the redox.

"a leaving group" - A leaving group is any atom or group of atoms that detaches from any chemical substance. There is no indication of its source and/or identity.

"the amino group of compounds (IX)" - It is not possible to determine if this term means that compound (IX) is intended to be an amine itself, or if compound (IX) is somehow to be modified to have an additional amine group.

"the halogen derivative" - Fails to define the intended reactant and has no specific set meaning. The term "derivative" may mean a residue or a different compound derived from the recited guanidine compound, and it is therefore not possible to know which derivatives are envisaged as derived from the illustrated compounds. The term "derivative" can refer to a compound that is formed from a similar compound or a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms. "Derivative" is of unknown scope.

"a reactive –Z-W derivative" – This fails to define the intended reactant. "Reactive" merely refers to a process that results in the interconversion of chemical substances. The term derivative has been discussed above.

The substituents P, Pg and L are undefined. In compound (VI) the symbol between the side-chain double bond and the adjacent oxygen is not understood. It should be explained or replaced by standard terminology.

Objected Claims

Claims 1-2, 4, 10 and 12-17 are objected to as directed to both elected and non-elected subject matter. The claims should be limited to only elected subject matter.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-

272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

Cecilia M. Jaisle, J.D.
5/18/2008